REMARKS

By this amendment, claims 23, 32, 40, 43-47, 57 and 65 are amended as discussed below. Claims 23-69 are pending. Support for the amendments can be found in the application, for example at page 7, lines 3 and 4 and in the previous claims set. No issue of new matter arises.

Claim objections

Claims 40, 43-47, 58 and 65 were objected to with suggestions by the Examiner to correct typographic errors or to improve antecedent basis. The alleged error "renaturatlon" was not found in claim 58. The remaining claims are amended above in accordance with the Examiner's suggestions. Reconsideration and withdrawal of these objections are respectfully requested.

Rejections under 35 U.S.C. §112, first paragraph

Claims 23-42 and 57 were rejected as discussed below.

The phrase "effective concentration" of claim 23 was alleged to be indefinite. Claims 24-31, 33-39, 41 and 42 were rejected as ultimately depending therefrom. Applicants respectfully submit that the specification at page 2, lines 9-11 explains "effective concentration: "The effective concentration of a protein should be the proportion of the protein in a solution, which is correctly folded with respect to the biological *in vivo* function." With this guidance from the specification, the issue of indefiniteness is clearly obviated. Reconsideration and withdrawal of this rejection are respectfully requested.

In claims 40 and 65, the phrase "further comprising the renaturation of the heterologous protein" was questioned with respect to "optional disruption of the microorganism". Applicants respectfully traverse the explained rationale underlying this rejection, but have amended the claims to recite ". . . wherein the protein has been denatured, said process comprising renaturation of the heterologous protein . . .". The traversal is with respect to the possible confusion of the microorganism with the protein. Disrupting a microorganism is independent from denaturating a protein. Applicants further respectfully suggest that no issue of undue experimentation would arise as the skilled artisan would be aware that renaturation would not be

necessary when denaturation had not occurred. Nevertheless, since the scope of the claims is not believed to be changed by amendment the claims are amended as indicated. No issue of new matter arises.

Reconsideration and withdrawal of the 35 USC §112 rejections are respectfully requested.

Double Patenting

Applicants gratefully acknowledge the withdrawal of the double patenting rejection.

35 USC §102 rejection

Claims 23-24, 33-37, 43-49 and 58-62 were rejected under 35 USC §102 over Ho. The Office action alleges Ho to teach an amino acid concentration in the range of 1-100 mM. Claims 23 and 43 recite "adding an amount of cysteine to make the concentration of cysteine between 150 and 220 mM". Support for this amendment can be found in the specification as filed, for example at page 7, lines 3 and 4. No issue of new matter arises. Accordingly, Ho cannot be said to teach the presently claimed invention. Reconsideration and withdrawal of this rejection are respectfully requested.

35 USC §103 rejection

Claims 25-32, 39, 40, 50-57, 64, 65, 68 and 69 were rejected under 35 USC §103 over Ho as applied to claims 23-24, 33-37, 43-49 and 58-62 rejected under 35 USC §102 above in further view of Eaton. As discussed above, Ho cannot properly be alleged to teach all the limitations of the claims.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. MPEP §2143.

Eaton is alleged to teach making heterologous protein. No allegation is made with respect to cysteine concentration. Therefore it cannot be said that the prior art references as applied teach or suggest all the claim limitations. Cysteine when exemplified in Table 5, columns 15 and 16, is only disclosed at 8 mM, clearly not suggestive of the instantly claimed range. Applicants respectfully submit that no *prima facie* case of obviousness is established. Reconsideration and withdrawal of this rejection are respectfully requested.

Furthermore, Ho can be seen as teaching away from the present invention. For example in columns 15 and 16, TABLE 5 – continued, in Set B, cysteine is listed as the 7th entry. Stability was poor (as seen from the Assay and Purity columns). Ho summarizes the results as follows: "The results presented in Table 5 demonstrate that the addition of amino acids such as methionine, arginine, lysine and glutamic acid provides protection against degradation of the CRF peptide in a liquid formulation." Bottom of columns 15 and 16.

Taken together, the poor results and the summarizing statement that omits mention of cysteine, appear to teach away from using cysteine. Since there is no teaching or suggestion to use cysteine to delay decrease in effective concentration of a protein and no teaching to use the instantly claimed concentration range of cysteine, the present invention cannot properly be said to be obvious over the applied references individually or in combination. Furthermore, the data and statements of Ho appear to teach away from the instant invention. For at least this additional reason, the instant invention should not be considered obvious. Reconsideration and withdrawal of the rejections over Ho and Ho in view of Eaton are respectfully requested.

Conclusion

In view of the above amendments and remarks, Applicants respectfully request reconsideration and withdrawal of all pending objections and rejections. Applicants respectfully submit that the application is now in condition for allowance and request prompt issuance of a Notice of Allowance. Should the Examiner believe that anything further is desirable that might put the application in even better condition for allowance, the Examiner is requested to contact the undersigned at the telephone number listed below.

Fees

No fees not otherwise provided for are believed to be necessitated by the instant response. However, should this be in error, authorization is hereby given to charge Deposit Account no. 18-1982 for any underpayment, or to credit any overpayments

Respectfully submitted,

George S. Jones

George S. Jones, Reg. No. 38,508
Attorney for Applicant

sanofi aventis U.S. Inc.
Patent Department
Route #202-206 / P.O. Box 6800
Bridgewater, NJ 08807-0800
Telephone (908) 231-3776
Telefax (908) 231-2626

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